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Abstract: Background: The prognostic score of the International Germ Cell Cancer Collaborative Group (IGCCCG) in metastatic germ-cell cancers (mGCC) relies on treatments delivered before 1990. It is unclear, if this score is still relevant to contemporary cohorts of patients who receive modern-type chemotherapy and supportive care. Patients and Methods: All patients who underwent cisplatin/etoposide based first-line chemotherapy for mGCC at the University Hospital Zurich (USZ) between 1991 and 2016 were identified retrospectively. Clinical characteristics were extracted from medical charts and patients classified according to the IGCCCG score (J Clin Oncol 1997;15:594). Progression-free survival (PFS) and overall survival (OS) probabilities at 5 years served as outcome parameters. Results: The study cohort consisted of 204 patients at a median age of 32 years and a median follow-up of 4.2 years. According to the IGCCCG score, PFS in the contemporary USZ cohort was 71% overall; 83% for good risk, 69% for intermediate risk and 30% for poor risk patients, $p < 0.001$. OS for the entire cohort was 88%. In respect to OS, we observed no difference between good risk and intermediate risk patients (94% vs. 91%, $p = 0.62$), but a statistically significant difference between those two risk groups and poor risk patients, who had an OS of only 65%, $p < 0.001$. Conclusions: Within the contemporary USZ cohort of mGCC patients no improvements in PFS probabilities were observed compared to the ones predicted by the IGCCCG score for any prognostic category, but marked improvements in OS probabilities for intermediate risk and poor risk patients, possibly due to better salvage treatments.

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Improved survival in metastatic germ-cell cancer

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Keywords: germ-cell cancer; chemotherapy; first-line treatment; survival; prognosis

Abstract

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Patients and Methods: All patients who underwent cisplatin/etoposide based first-line chemotherapy for mGCC at the University Hospital Zurich (USZ) between 1991 and 2016 were identified retrospectively. Clinical characteristics were extracted from medical charts and patients classified according to the IGCCCG score *(J Clin Oncol 1997;15:594).* Progression-free survival (PFS) and overall survival (OS) probabilities at 5 years served as outcome parameters.

Results: The study cohort consisted of 204 patients at a median age of 32 years and a median follow-up of 4.2 years. According to the IGCCCG score, PFS in the contemporary USZ cohort was 71% overall; 83% for good risk, 69% for intermediate risk and 30% for poor risk patients, $p<0.001$. OS for the entire cohort was 88%. In respect to OS, we observed no difference between good risk and intermediate risk patients (94% vs. 91%, $p=0.62$), but a statistically significant difference between those two risk groups and poor risk patients, who had an OS of only 65%, $p<0.001$.

Conclusions: Within the contemporary USZ cohort of mGCC patients no improvements in PFS probabilities were observed compared to the ones predicted by the IGCCCG score for any prognostic category, but marked improvements in OS probabilities for intermediate risk and poor risk patients, possibly due to better salvage treatments.

Introduction

In 2017, an estimated number of 8,850 new cases of germ-cell cancers (GCC) will be diagnosed in the United States. [1] Although GCC show a high sensitivity to cisplatin-based chemotherapy, 10-15% of patients fail first-line treatment and 3-5% of all GCC patients will eventually die of their disease. [2] In 1997, the International Germ-Cell Cancer Cooperative Group (IGCCCG) published a prognostic classification for metastatic GCC (mGCC) to direct and optimize treatments. [3] The resulting IGCCCG score has become the reference for treatment decisions in mGCC ever since. However, as the IGCCCG score relies on treatments delivered between 1975 and 1990 and as diagnostic and therapeutic standards as well as supportive care have improved substantially since that time, this study aimed to assess the performance of the IGCCCG score in a contemporary patient cohort.

Patients and methods

All patients who underwent first-line chemotherapy at the University Hospital Zurich (USZ) between 1991 and 2016 for mGCC were identified. Inclusion criteria for the analysis were modern type combination chemotherapy consisting of at least three or more cycles of cisplatin and etoposide with or without bleomycin or ifosfamide. The year 1991 war chosen as a starting point for the analysis as the combination of cisplatin, etoposide and bleomycin (BEP) was routinely used at the USZ since the publication of Williams et al demonstrating superiority of BEP over the vinblastine contaning combination in 1987. [4] Bleomycin was either omitted or replaced by ifosfamide in the event of contraindications to this drug. Also high-dose chemotherapy using carboplatin and etoposide was introduced in 1990 as salvage treatment at the USZ after the initial publication of Nichols et al. [5]

All patients with residual tumors after chemotherapy were routinely scheduled for post-chemotherapy surgery. Patients with relapse or progression after first-line treatment were

scheduled for salvage treatment based individually on relapse presentation and risk factors at the time.

We extracted clinical characteristics such as age at diagnosis, location of primary tumor, histology, location of metastases, levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) from electronic medical charts and calculated the individual IGCCCG score for each patient. [3] The study was approved by the local ethics committee (STV KEK-ZH 25-2008).

The endpoints of the study were the progression-free survival (PFS) and overall survival (OS) probabilities at 5 years. PFS started with the initiation of chemotherapy and ended with progression or death, whichever occurred first. OS started with the initiation of chemotherapy and ended with the death of a patient. Survival status was identified from medical charts or death certificates. Patients without an event were censored at the date of last follow-up.

PFS and OS were calculated according to the Kaplan-Meier method and compared using the log-rank test. Survival probabilities are reported together with the corresponding standard error (SE) and 95% confidence intervals (95% CI). Statistical analyses were performed using the STATA software Version 10.0 (StataCorp LLC, College Station, Texas, USA). Continuous non-normally distributed variables are presented as median and interquartile ranges (IQR) and categorical variables are presented as percentages. Probabilities $p < 0.05$ were considered statistically significant. All statistical tests were two-sided.

Results

Patients characteristics

The final study cohort consisted of 204 patients at a median age of 32 years (IQR 26-39 years) and median follow-up time of 4,2 years (IQR 1,9-7,8 years) (Table 1). Among 195 patients with known histological subtype, 52/195 (27%) patients had pure seminoma and

143/195 (73%) had non-seminoma or mixed histologies. Details of other patient characteristics are shown as table 1.

The contemporary USZ cohort was comparable to the historical IGCCCG cohort. Imbalances were found for the number of seminoma patients and patients with mediastinal primary tumors, which were more frequent in the contemporary cohort. Patients with brain metastases were more frequent in the historical cohort.

Despite these imbalances, the historical IGCCCG and the contemporary USZ cohort showed similar distributions in respect to the IGCCCG risk groups, with 60% versus 62% low risk patients, 26% versus 19% intermediate risk patients and 14% versus 19% poor risk patients, respectively. Compared to the historical IGCCCG cohort less intermediate risk and slightly more good risk and poor risk patients were observed (Table 2).

In the contemporary USZ cohort treatment consisted of three or four cycles of BEP in 184/204 (90%) patients, cisplatin and etoposide (EP) in 6/204 (3%) patients, cisplatin, etoposide and ifosfamide in 8/204 (4%) patients and other cisplatin- and etoposide-based regimens in 6/204 (3%) patients. Overall 57/204 (28%) relapses occurred, 9/52 (17%) among patients with pure seminoma, and 48/143 (34%) among patients with non-seminoma or mixed histologies. Salvage treatment in relapsed patients consisted of surgery alone in 12/57 (21%) patients with teratoma, conventional-dose cisplatin-based chemotherapy (CDCT) in 13/57 (23%) patients, sequential high-dose chemotherapy (HDCT) with carboplatin and etoposide in 23/57 (40%) patients, and CDCT followed by HDCT in 7/57 (12%) patients. Two patients died before any salvage treatment could be given (table 3). Residual tumor resections after completion of salvage chemotherapy were performed in 17/43 (40%) patients. OS in relapsing as compared to non-relapsing patients is shown as supplemental figure S1.

Survival

The published IGCCCG score correctly divided the contemporary USZ cohort into three distinct and significantly different groups for PFS with probabilities of 83% (SE: 3.6%; 75% CI: 85% to 89%), 69% (SE: 8%; 95% CI: 50% to 82%) and 30% (SE: 10%; 95% CI: 13% to 50%) at 5 years ($p<0.001$) (Figure 1). These probabilities are very similar to the predicted ones according to the published IGCCCG score (Table 2).

The OS probabilities in the contemporary USZ cohort were 95% (SE: 2.1%; 95% CI: 89% to 98%), 91% (SE: 4.8%; 95% CI: 76% to 97%), and 65% (SE: 8.9%; 95% CI: 44% to 79%) for good risk, intermediate risk and poor risk patients, respectively. Compared to the OS probabilities predicted by the published IGCCCG score, this represents a marked improvement in OS among intermediate and poor risk patients, and only a slight improvement among good risk patients in the contemporary USZ cohort (Figure 2). In respect to OS, the IGCCCG score did no longer predict separate probabilities for the groups of good and intermediate risk patients ($p=0.62$). Only OS for poor risk patients was correctly predicted by the historical IGCCCG score with a significantly inferior OS probability compared to good and intermediate risk patients ($p<0.001$).

Discussion

Substantial improvements in diagnostic and therapeutic standards have occurred since the introduction of cisplatin into the treatment of mGCC. Our present retrospective analysis, however, demonstrated that the observed PFS probabilities for mGCC after first-line chemotherapy did not differ compared to the ones predicted by the IGCCCG score despite these improvements. Although, the IGCCCG score, which was developed based on treatments delivered between 1975 and 1990, still correctly divided our more contemporary USZ cohort treated between 1991 and 2016 into three risk groups based on their PFS, the PFS probabilities within these three risk groups have not improved. Possibly the efficacy of

cisplatin-based treatment had already been high in the IGCCCG cohort so that further improvements might have been too small to be detected, the rate of treatment-related deaths might have been too low and the contemporary patient cohort studied too small to detect any improvements in first-line treatment that may have occurred since 1990. Treatment intensification using dose-dense or upfront high-dose chemotherapy in poor risk patients, in whom most of the benefit of treatments intensification can be expected, had not been used during the study period at our center. [6]

In contrast, the observed OS probabilities have markedly improved particularly among intermediate risk and poor risk patients in the contemporary USZ cohort as compared to the OS probabilities predicted by the IGCCCG score. The OS probabilities at 5 years increased from 91% as predicted to 95% observed among good risk patients, from 79% as predicted to 91% observed among intermediate risk patients and from 48% as predicted to 65% observed among poor risk patients. With these improvements the observed OS probabilities among the IGCCCG risk groups were no longer different between the good and intermediate risk patients ($p=0.62$), but still significantly different between those two risk groups and poor risk patients ($p<0.001$). The comparison of the probabilities for PFS and OS as predicted by the published IGCCCG score and the ones observed in our contemporary USZ cohort produced three important findings.

First, the IGCCCG score is no longer prognostic for OS among intermediate risk patients. In our contemporary USZ cohort the good risk and intermediate risk groups showed similar OS probabilities indicating that the IGCCCG score no longer separates these two risk groups sufficiently well. Modifications of the published IGCCCG score with better discrimination of intermediate risk and poor risk patients have been suggested in an attempt to avoid overtreatment as well as undertreatment of mGCC patients. [11]

Second, since early 1970, improvements in diagnosis and treatment of GCC have mainly consisted in better staging using computed tomography (CT) and magnetic resonance tomography (MRT) scans as well as improved supportive care. Apart from etoposide with superior activity compared to vinblastine, no new active agent has been introduced into the standard first-line treatment of mGCC. [4] Therefore the current recommendation for first-line treatment remains three to four cycles BEP or EP depending on the IGCCCG risk group. [7-10] Very recently only, intensive dose-dense combination chemotherapy has demonstrated superior PFS, but not OS in a cohort of poor-risk patients with an unfavorable marker decline after the first-cycle of BEP. [6] While current improvements in supportive care have certainly improved tolerability of cisplatin-based combination treatment, our data demonstrates comparable PFS probabilities between the PFS as predicted by the IGCCCG score and the observed PFS in our contemporary USZ cohort. This confirms the limited improvements in efficacy of conventional-dose first-line treatments of mGCC since early 1970.

Third, there are several explanations for an improved OS in mGCC patients in our more contemporary cohort. Better diagnostic tools and structured follow-up schedules might have resulted in the earlier diagnosis of relapses occurring in patients with less advanced disease. Improvements in supportive care with better management of infectious complications, less treatment delays due to the availability of hematopoietic growth factors as well as more experience in the management of organ toxicities might have had a greater impact after the more toxic salvage as compared to the less toxic first-line treatment. However, the biggest contribution to the improvements in OS comes from better salvage strategies that have changed substantially since 1990. Conventional-dose first salvage chemotherapy has integrated new drugs with single agent activity in cisplatin-refractory patients such as ifosfamide and paclitaxel. [12,13] High-dose chemotherapy is being used more regularly as first or subsequent salvage treatment. [14,15] Salvage surgery is being applied more

aggressively. [16] And finally effective third-line treatment options have become available integrating gemcitabine and oxaliplatin with reported long-term survivors even in prognostically unfavorable groups of patients. [17] With the lack of prospective randomized trials, however, it will be impossible to dissect the individual contribution of each of these interventions, which are all reflected in our contemporary patient cohort studied.

The present analysis is limited by its retrospective design, single center approach and small sample size. Moreover, we were only able to compare the survival probabilities predicted by the IGCCC score to the ones actually observed at our center. As we did not have access to the original IGCCCG data, we cannot make, and did not intend to perform direct comparisons between the initial IGCCCG cohort and our contemporary patient cohort. Patients referred to a tertiary cancer center will always be selected and will not be representative for the population of all mGCC patients. An analysis of a larger, less selected and multicenter cohort and a comparison to the original IGCCCG data might result in different findings. However, almost identical results have been presented from Germany at the meeting of the European Society of Medical Oncology among patients treated within a community service. [18] Finally, unknown confounders other than the ones mentioned above may have impacted on the better OS probabilities observed in the contemporary USZ cohort. However, despite these shortcomings the present analysis is hypothesis generating and provides the rationale for an ongoing international multi-center effort to study the results of modern type chemotherapy in a much larger and less selected patient cohort of mGCC.

Key Messages

We assessed the performance the prognostic score of the International Germ-Cell Cancer Collaborative Group (IGCCCG) in a contemporary patient cohort. The observed PFS probabilities were not different to the ones predicted. In contrast, the observed OS

probabilities had markedly improved particularly in intermediate and poor risk patients most likely as a result of better salvage treatments.

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Disclosures

None of the authors has any disclosures or conflict-of-interest related to this submission.

Figure 1: Progression-free survival probabilities in the contemporary cohort of the University Hospital Zurich (n=204)

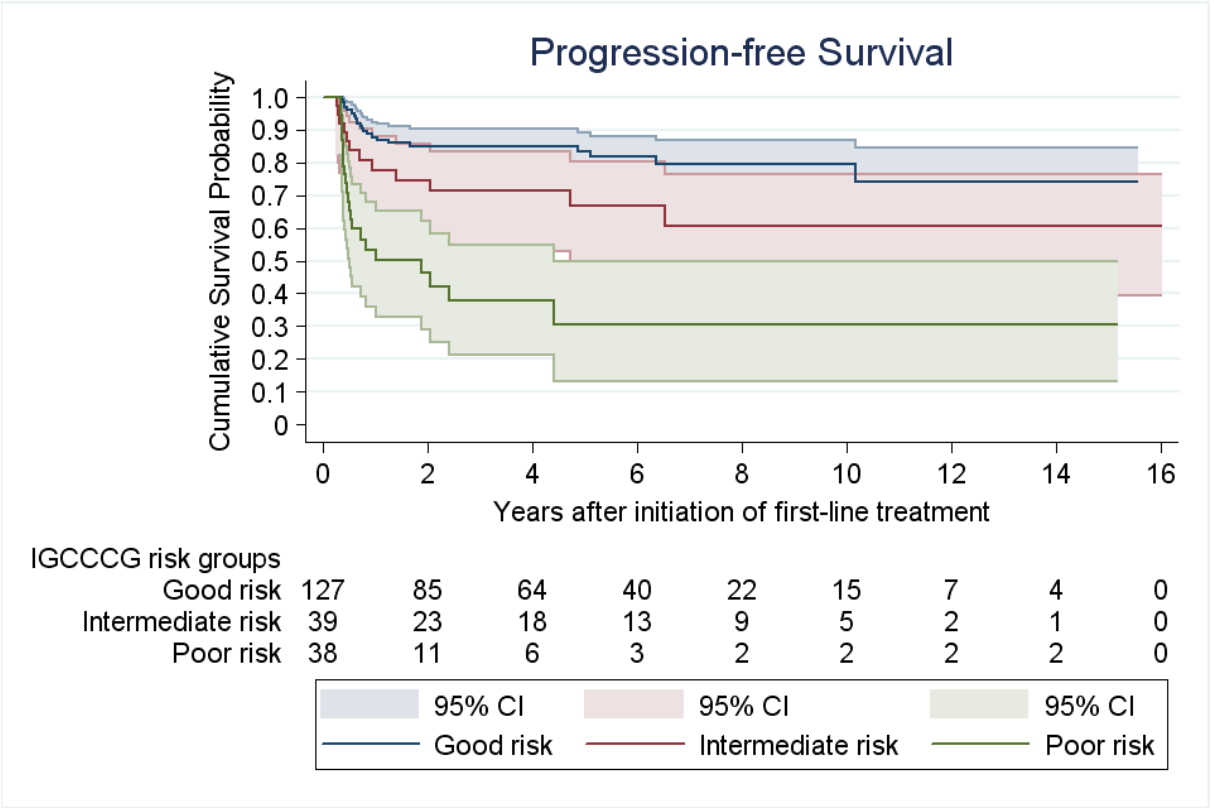

Figure 2: Overall survival probabilities in the contemporary cohort of the University Hospital Zurich (n=204)

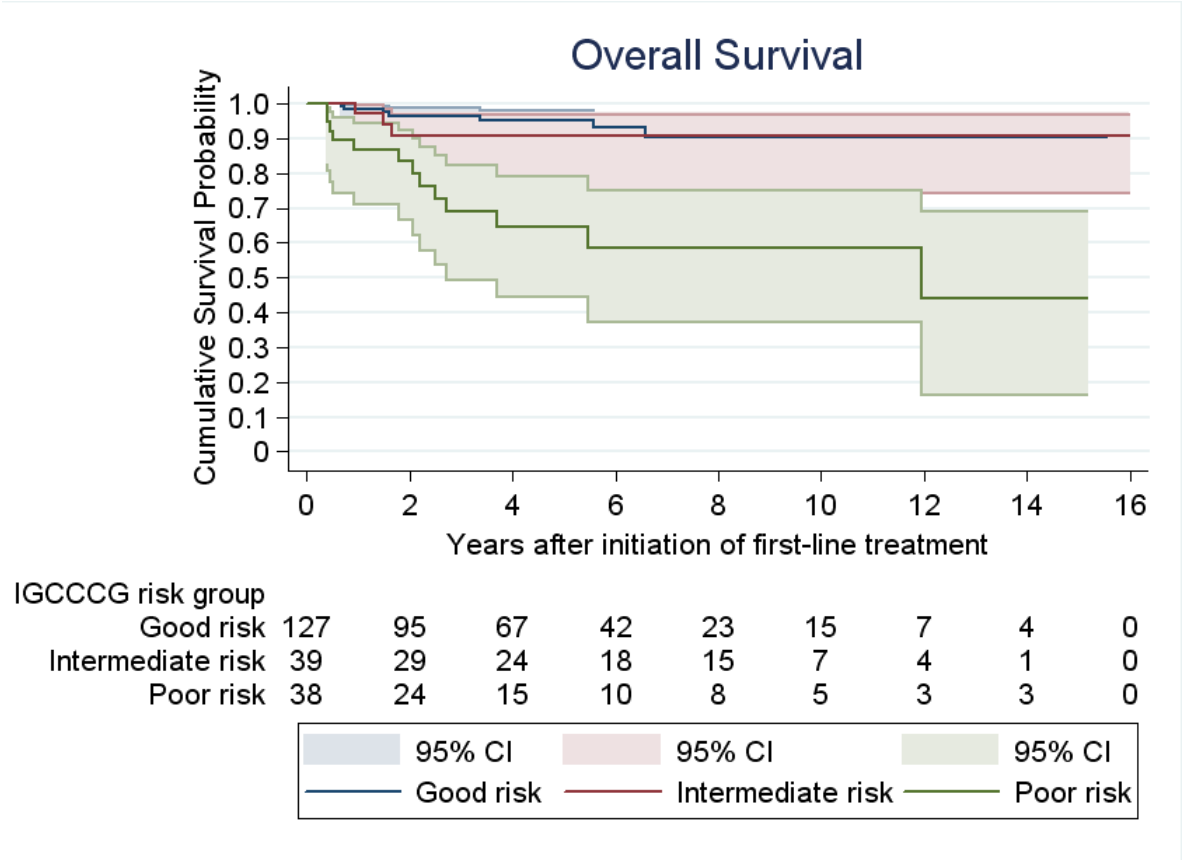

Figure S1: Overall survival probabilities in patients with (n=147) and without (n=57) progression after first-line treatment

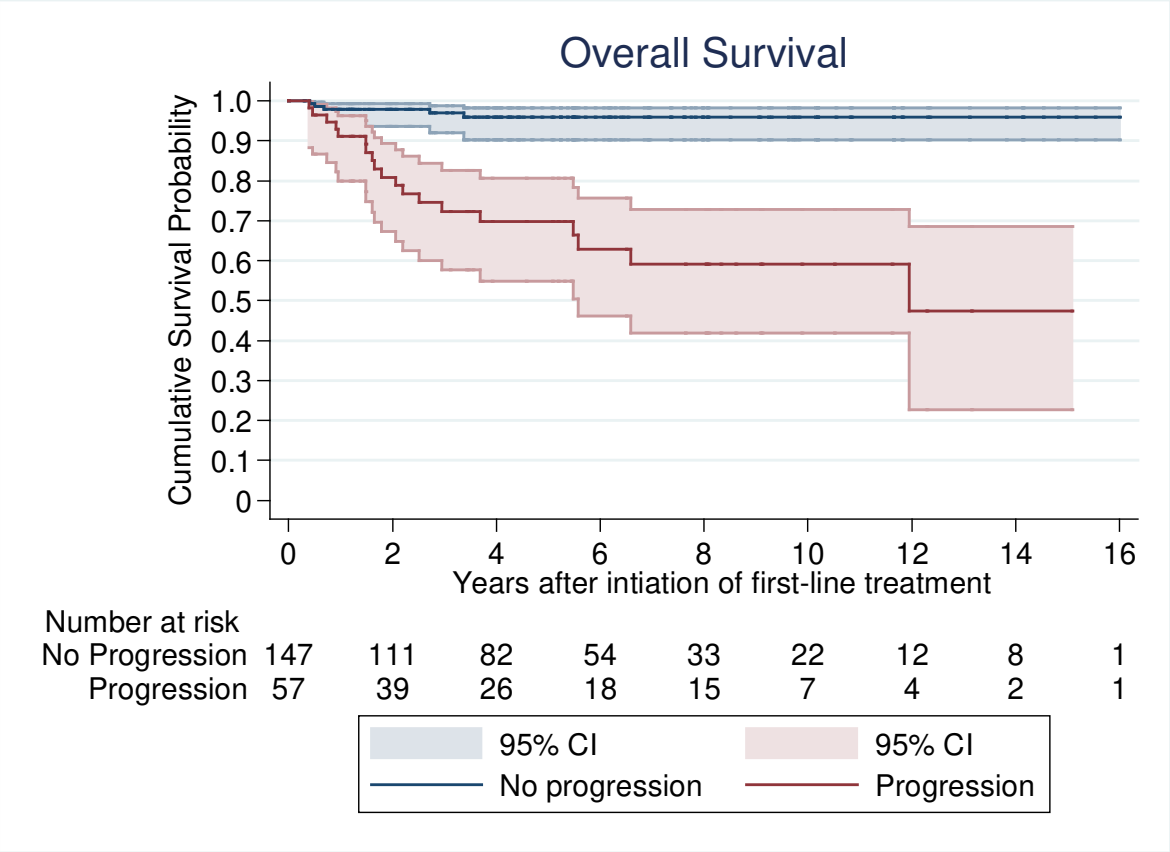

Table 1: Comparison of patient characteristics of the published IGCCCG cohort and the contemporary cohort

	IGCCCG cohort *n=5889* (1975-1990)	**USZ cohort *n=204*** (1991-2016)
Age	5862/5889	204/204
<20	562 (10%)	10 (5%)
20-29	2808 (48%)	72 (35%)
30-39	1674 (28%)	73 (36%)
40-49	573 (10%)	38 (19%)
≥50	272 (4%)	11 (5%)
Primary tumor	5862/5889	204/204
Gonadal	5423/5862 (93%)	171/204 (84%)
Extragonadal	439/5862 (7%)	33/204 (16%)
Histology	5862/5889	195/204
Seminoma	660/5862 (11%)	52/195 (27%)
Non-Seminoma or mixed	5202/5862 (89%)	143/195 (73%)
Location of metastases		
Abdominal	3705/5060 (73%)	176/204 (86%)
Mediastinal	610/5091 (12%)	60/202 (29%)
Neck mass	570/5022 (11%)	26/201 (13%)
Lung	3375/5712 (40%)	80/203 (39%)
Liver	360/5784 (6%)	14/204 (7%)
Bone	85/5574 (2%)	9/203 (4%)
Brain	870/5572 (16%)	6/203 (3%)
AFP	5748/5889	128/204
<1000	4275/5748 (86%)	112/128 (87%)
1000-10.000	602/5748 (10%)	13/128 (10%)
>10.000	211/5748 (4%)	3/128 (2%)
HCG	5769/5889	133/204
<1000	5072/5769 (88%)	98/133 (73%)
1000-10.000	384/5769 (7%)	17/133 (13%)
>10.000	313/5769 (5%)	18/133 (14%)
LDH	3720/5889	115/204
<1.5x upper limit	2413/3720(65%)	81/115 (70%)
1.5-10x upper limit	1245/3720 (33%)	33/115 (29%)
>10x upper limit	62/3720 (2%)	1/115 (1%)
IGCCCG risk groups		
Good	n.a. (60%)	127/204 (62%)
Intermediate	n.a. (26%)	39/204 (19%)
Poor	n.a. (14%)	38/204 (19%)

USZ = University Hospital Zurich; AFP = Alpha-fetoprotein; HCG = Human chorionic gonadotropin, IGCCCG = International; Germ Cell Cancer Collaborative Group, LDH = Lactat dehydrogenase; n.a. = not available

Table 2: **Comparison of progression free survival (PFS) and overall survival (OS) probabilities as predicted by the IGCCCG score and the ones observed in the contemporary USZ cohort**

	Good risk		**Intermediate risk**		**Poor risk**	
	Predicted by the IGCCCG score	Observed in the USZ cohort *(n=127)*	Predicted by the IGCCCG score	Observed in the USZ cohort *(n=39)*	Predicted by the IGCCCG score	Observed in the USZ cohort *(n=38)*
Treatments	**(1975-1990)**	**(1991-2016)**	**(1975-1990)**	**(1991-2016)**	**(1975-1990)**	**(1991-2016)**
Percent of entire cohort	60%	62%	26%	19%	14%	19%
PFS at 5 years	88%	83% (75%-89%)*	75%	69% (50%-82%)*	41%	30% (13%-50%)*
OS at 5 years	91%	95% (89%-98%)*	79%	91% (76%-97%)*	48%	65% (44%-79%)*

IGCCCG= International Germ Cell Cancer Collaborative Group *(J Clin Oncol 1997;15:594)*; USZ = University Hospital Zurich; * 95% confidence interval

Table 3: Salvage strategies after failure of first-line treatment *

Salvage strategy	Pat.	Surgery	Outcome
Only surgery	**12**	-	11 alive and in remission 1 lost-to follow
CDCT	**13**	no	3 alive and in remission 4 died
		yes	2 alive and in remission 1 alive with disease 3 died
HDCT	**23**	no	11 alive and in remission 1 lost-to-follow 4 died
		yes	4 alive and in remission 1 lost-to-follow 2 died
CDCT and HDCT	**7**	no	3 died
		yes	1 alive and in remission 3 died
	2		2 died before treatment

Legend: Pat. = number of patients; CDCT = conventional-dose chemotherapy; HDCT = high-dose chemotherapy; remission = complete remission or partial remission with negative serum tumor markers.

* Overall survival probabilities in relapsing as compared to non-relapsing patients are shown as supplemental figure S1.